

Manganese

Manganese is a mineral element that is both nutritionally essential and potentially toxic. The derivation of its name from the Greek word for magic remains appropriate because scientists are still working to understand the diverse effects of manganese deficiency and manganese toxicity in living organisms.

Function

Manganese (Mn) plays an important role in a number of physiologic processes as a constituent of some enzymes and an activator of other enzymes.

Antioxidant function

Manganese superoxide dismutase (MnSOD) is the principal antioxidant enzyme in the mitochondria. Because mitochondria consume over 90% of the oxygen used by cells, they are especially vulnerable to oxidative stress. The superoxide radical is one of the reactive oxygen species produced in mitochondria during ATP synthesis. MnSOD catalyzes the conversion of superoxide radicals to hydrogen peroxide, which can be reduced to water by other antioxidant enzymes.

Metabolism

A number of manganese-activated enzymes play important roles in the metabolism of carbohydrates, amino acids, and cholesterol. Pyruvate carboxylase, a manganese-containing enzyme, and phosphoenolpyruvate carboxykinase (PEPCK), a manganese-activated enzyme, are critical in gluconeogenesis—the production of glucose from non-carbohydrate precursors. Arginase, another manganese-containing enzyme, is required by the liver for the urea cycle, a process that detoxifies ammonia generated during amino acid metabolism.

Bone development

Manganese deficiency results in abnormal skeletal development in a number of animal species. Manganese is the preferred cofactor of enzymes called glycosyltransferases; these enzymes are required for the synthesis of proteoglycans that are needed for the formation of healthy cartilage and bone.

Wound healing

Wound healing is a complex process that requires increased production of collagen. Manganese is required for the activation of prolidase, an enzyme that functions to provide the amino acid, proline, for collagen formation in human skin cells. A genetic disorder known as prolidase deficiency results in abnormal wound healing among other problems, and is characterized by abnormal manganese metabolism. Glycosaminoglycan synthesis, which requires manganese-activated glycosyltransferases, may also play an important role in wound healing.

Nutrient interactions

Iron

Although the specific mechanisms for manganese absorption and transport have not been determined, some evidence suggests that iron and manganese can share common absorption and transport pathways. Absorption of manganese from a meal decreases as the meal's iron content increases. Iron supplementation (60 mg/day for four months) was associated with decreased blood manganese levels and decreased MnSOD activity in white blood cells, indicating a reduction in manganese nutritional status. Additionally, an individual's iron status can affect manganese bioavailability. Intestinal absorption of manganese is increased during iron deficiency, and increased iron stores (ferritin levels) are associated with decreased manganese absorption. Men generally absorb less manganese than women; this may be related to the fact that men usually have higher iron stores than women.

Magnesium

Supplemental magnesium (200 mg/day) has been shown to slightly decrease manganese bioavailability in healthy adults, either by decreasing manganese absorption or by increasing its excretion.

Calcium

In one set of studies, supplemental calcium (500 mg/day) slightly decreased manganese bioavailability in healthy adults. As a source of calcium, milk had the least effect, while calcium carbonate and calcium phosphate had the greatest effect. Several other studies have found minimal effects of supplemental calcium on manganese metabolism.

Deficiency

Manganese deficiency has been observed in a number of animal species. Signs of manganese deficiency include impaired growth, impaired reproductive function, skeletal abnormalities, impaired glucose tolerance, and altered carbohydrate and lipid metabolism. In humans, demonstration of a manganese deficiency syndrome has been less clear. A child on long-term total parenteral nutrition (TPN) lacking manganese developed bone demineralization and impaired growth that were corrected by manganese supplementation. Young men who were fed a low-manganese diet developed decreased serum cholesterol levels and a transient skin rash. Blood calcium, phosphorus, and alkaline phosphatase levels were also elevated, which may indicate increased bone remodeling as a consequence of insufficient dietary manganese. Young women fed a manganese-poor diet developed mildly abnormal glucose tolerance in response to an intravenous (IV) infusion of glucose.

The Adequate Intake (AI)

Because there was insufficient information on manganese requirements to set a Recommended Dietary Allowance (RDA), the Food and Nutrition Board (FNB) of the Institute of Medicine set an adequate intake level (AI). Because overt manganese deficiency has not been documented in humans eating natural diets, the FNB based the AI on average dietary intakes of manganese determined by the

Total Diet Study—an annual survey of the mineral content of representative diets. AI values for manganese are listed in the table below in milligrams (mg)/day by age and gender.

Adequate Intake (AI) for Manganese			
Life Stage	Age	Males (mg/day)	Females (mg/day)
Infants	0-6 months	0.003	0.003
Infants	7-12 months	0.6	0.6
Children	1-3 years	1.2	1.2
Children	4-8 years	1.5	1.5
Children	9-13 years	1.9	1.6
Adolescents	14-18 years	2.2	1.6
Adults	19 years and older	2.3	1.8
Pregnancy	all ages	-	2.0
Breastfeeding	all ages	-	2.6

Disease Prevention

Low dietary manganese and low levels of manganese in blood or tissue have been associated with several chronic diseases. Although manganese insufficiency is not currently thought to cause the diseases discussed below, more research may be warranted to determine whether suboptimal manganese nutritional status contributes to certain disease processes.

Osteoporosis

It has been documented that women with osteoporosis have decreased plasma levels of manganese and also an enhanced plasma response to an oral dose of manganese. This suggests that osteoporotic women may have lower manganese status than women without osteoporosis. A study in healthy postmenopausal women

found that a supplement containing manganese (5 mg/day), copper (2.5 mg/day), and zinc (15 mg/day) in combination with a calcium supplement (1,000 mg/day) was more effective than the calcium supplement alone in preventing spinal bone loss over a two-year period. However, the presence of other trace elements in the supplement makes it impossible to determine whether manganese supplementation was the beneficial agent for maintaining bone mineral density.

Diabetes mellitus

Manganese deficiency results in glucose intolerance similar to diabetes mellitus in some animal species, but studies examining the manganese status of diabetic humans have generated mixed results. In one study, whole blood manganese levels did not differ significantly between 57 diabetics and 28 non-diabetic controls. However, urinary manganese excretion tended to be slightly higher in 185 diabetics compared to 185 non-diabetic controls. Additionally, a study of functional manganese status found the activity of the antioxidant enzyme, MnSOD, was lower in the white blood cells of diabetics than in those of non-diabetics. Neither 15 mg nor 30 mg of oral manganese improved glucose tolerance in diabetics or non-diabetic controls when given at the same time as an oral glucose challenge.

More recently, a case-control study of 250 diabetic and non-diabetic individuals found that type 2 diabetic individuals had higher serum manganese levels than non-diabetics. Although manganese appears to play a role in glucose metabolism, there is little evidence that manganese supplementation improves glucose tolerance in diabetic or non-diabetic individuals.

Epilepsy (seizure disorders)

Manganese deficient rats are more susceptible to seizures than manganese sufficient rats, and rats that are genetically prone to epilepsy have lower than normal brain and blood manganese levels. Certain subgroups of humans with epilepsy reportedly have lower

whole blood manganese levels than non-epileptic controls. One study found blood manganese levels of individuals with epilepsy of unknown origin were lower than those of individuals whose epilepsy was induced by trauma (e.g., head injury) or disease, suggesting a possible genetic relationship between epilepsy and abnormal manganese metabolism. While manganese deficiency does not appear to be a cause of epilepsy in humans, the relationship between manganese metabolism and epilepsy deserves further research.

Food sources

People eating vegetarian diets and diets emphasizing whole grains may have manganese intakes as high as 10.9 mg/day. Rich sources of manganese include whole grains, nuts, leafy vegetables, and teas. Foods high in phytic acid, such as beans, seeds, nuts, whole grains, and soya products, or foods high in oxalic acid, such as cabbage, spinach, and sweet potatoes, may slightly inhibit manganese absorption. Although teas are rich sources of manganese, the tannins present in tea may moderately reduce the absorption of manganese. The manganese content of some manganese-rich foods is listed in milligrams (mg) in the table below. For more information on the nutrient content of foods, search the USDA food composition database.

Food	Serving	Manganese (mg)
Pineapple, raw	1/2 cup, diced	0.91
Pineapple juice	1/2 cup (4 ounces)	0.63
Pecans	1 ounce	1.28
Almonds	1 ounce	0.72
Peanuts	1 ounce	0.55
Instant oatmeal (prepared with water)	1 packet	1.68
Raisin bran cereal	1 cup	1.88

Brown rice, cooked	1/2 cup	0.88
Whole wheat bread	1 slice	0.60
Pinto beans, cooked	1/2 cup	0.39
Lima beans, cooked	1/2 cup	0.49
Navy beans, cooked	1/2 cup	0.48
Spinach, cooked	1/2 cup	0.84
Sweet potato, cooked	1/2 cup, mashed	0.50
Tea (green)	1 cup (8 ounces)	0.41-1.58
Tea (black)	1 cup (8 ounces)	0.18-0.77

Supplements

Several forms of manganese are found in supplements, including manganese gluconate, manganese sulfate, manganese ascorbate, and amino acid chelates of manganese. Manganese is available as a stand-alone supplement or in combination products. Relatively high levels of manganese ascorbate may be found in a bone/joint health product containing chondroitin sulfate and glucosamine hydrochloride.

Safety

Toxicity

Inhaled manganese

Manganese toxicity may result in multiple neurological problems and is a well-recognized health hazard for people who inhale manganese dust. Unlike ingested manganese, inhaled manganese is transported directly to the brain before it can be metabolized in the liver. The symptoms of manganese toxicity generally appear slowly over a period of months to years. In its worst form, manganese toxicity can result in a permanent neurological disorder with symptoms similar to those of Parkinson's disease, including tremors, difficulty walking, and facial muscle spasms. This syndrome is sometimes preceded by psychiatric symptoms, such as irritability, aggressiveness, and even hallucinations.

Methylcyclopentadienyl manganese tricarbonyl (MMT)

MMT is a manganese-containing compound used in gasoline as an anti-knock additive. Although it has been used for this purpose in Canada for more than 20 years, uncertainty about adverse health effects from inhaled exhaust emissions kept the U.S. Environmental Protection Agency (EPA) from approving its use in unleaded gasoline. In 1995, a U.S. court decision made MMT available for widespread use in unleaded gasoline. A recent study in Montreal, where MMT had been used for more than 10 years, found airborne manganese levels to be similar to those in areas where MMT was not used. However, the impact of long-term exposure to low levels of MMT combustion products has not been thoroughly evaluated and will require additional study.

Ingested manganese

Limited evidence suggests that high manganese intakes from drinking water may be associated with neurological symptoms similar to those of Parkinson's disease. Severe neurological symptoms were reported in 25 people who drank water contaminated with manganese, and probably other contaminants from dry cell batteries for two to three months. Water manganese levels were found to be 14 mg/liter almost two months after symptoms began and may have already been declining. A study of older adults in Greece found a high prevalence of neurological symptoms in those exposed to water manganese levels of 1.8-2.3 mg/liter, whereas a study in Germany found no evidence of increased neurological symptoms in people drinking water with manganese levels ranging from 0.3-2.2 mg/liter compared to that drinking water containing less than 0.05 mg/liter. Manganese in drinking water may be more bioavailable than manganese in food. However, none of the studies measured dietary manganese, so total manganese intake in these cases is unknown. In the U.S., the EPA recommends 0.05 mg/liter as the maximum allowable manganese concentration in drinking water.

A single case of manganese toxicity was reported in a person who took large amounts of mineral supplements for years, while another case was reported as a result of a person taking a Chinese herbal

supplement. Manganese toxicity resulting from foods alone has not been reported in humans, even though certain vegetarian diets could provide up to 20 mg/day of manganese.

Intravenous manganese

Manganese neuro-toxicity has been observed in individuals receiving parenteral nutrition, both as a result of excessive manganese in the solution and as an incidental contaminant.

Individuals with increased susceptibility to manganese toxicity

- *Chronic liver disease:* Manganese is eliminated from the body mainly in bile. Thus, impaired liver function may lead to decreased manganese excretion. Manganese accumulation in individuals with cirrhosis or liver failure may contribute to neurological problems and Parkinson’s disease-like symptoms.
- *Newborns:* The newborn brain may be more susceptible to manganese toxicity due to a greater expression of receptors for the manganese transport protein (transferrin) in developing nerve cells and the immaturity of the liver’s bile elimination system.

Due to the severe implications of manganese neuro-toxicity, the Food and Nutrition Board (FNB) of the Institute of Medicine set very conservative tolerable upper intake levels (UL) for manganese; the ULs are listed in the table below according to age.

Tolerable Upper Intake Level (UL) for Manganese	
Age Group	UL (mg/day)
Infants 0-12 months	Not possible to establish*
Children 1-3 years	2
Children 4-8 years	3
Children 9-13 years	6
Adolescents 14-18 years	9
Adults 19 years and older	11

*Source of intake should be from food and formula only.

Drug interactions

Magnesium-containing antacids and laxatives and the antibiotic medication, tetracycline, may decrease the absorption of manganese if taken together with manganese-containing foods or supplements.

High levels of manganese in supplements marketed for bone/joint health

Two recent studies have found that supplements containing a combination of glucosamine hydrochloride, chondroitin sulfate, and manganese ascorbate are beneficial in relieving pain due to mild or moderate osteoarthritis of the knee when compared to a placebo. The dose of elemental manganese supplied by the supplements was 30 mg/day for eight weeks in one study and 40 mg/day for six months in the other. No adverse effects were reported during either study, and blood manganese levels were not measured. Neither study compared the treatment containing manganese ascorbate to a treatment containing glucosamine hydrochloride and chondroitin sulfate without manganese ascorbate, so it is impossible to determine whether the supplement would have resulted in the same benefit without high doses of manganese.

Linus Pauling Institute Recommendation

The adequate intake (AI) for manganese (2.3 mg/day for adult men and 1.8 mg/day for adult women) appears sufficient to prevent deficiency in most individuals. The daily intake of manganese most likely to promote optimum health is not known. Following the Linus Pauling Institute recommendation to take a multivitamin / multimineral supplement containing 100% of the daily values (DV) of most nutrients will generally provide 2 mg/day of manganese in addition to that in foods. Because of the potential for toxicity and the lack of information regarding benefit, manganese supplementation beyond 100% of the DV (2 mg/day) is not recommended. There is presently no evidence that the consumption of a manganese-rich plant-based diet results in manganese toxicity.

Adults over the age of 65

The requirement for manganese is not known to be higher for older adults. However, liver disease is more common in older adults and may increase the risk of manganese toxicity by decreasing the elimination of manganese from the body. Manganese supplementation beyond 100% of the DV (2 mg/day) is not recommended.